

**Hospital Pharmacists
involved in ATMP and Risk
Assessment**



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Conflict of interest

Conflict of interest: nothing to disclose



PIC/S organization

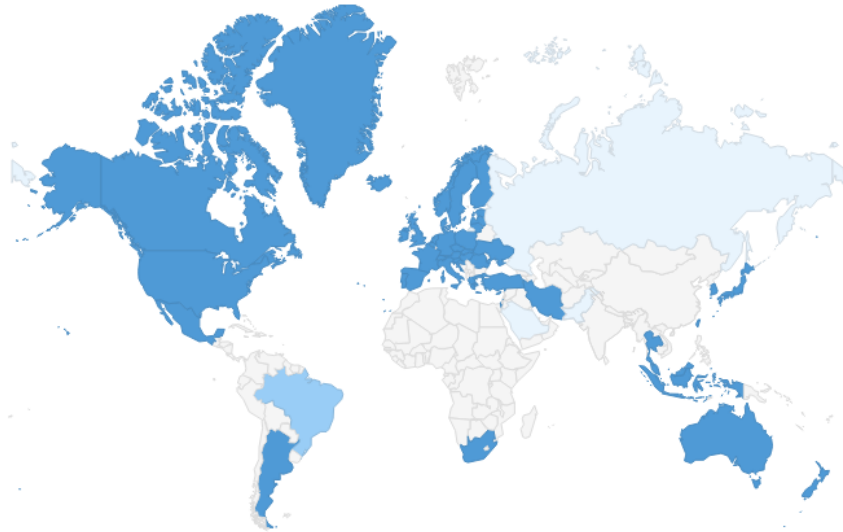
Goal: To lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products



PIC/S organization

- Developing and promoting harmonised GMP standards and guidance documents.
- Training competent authorities, in particular GMP inspectors.
- Assessing (and reassessing) GMP Inspectorates.
- Facilitating the co-operation and networking for competent authorities and international organisations.

PIC/S organization



Currently 52 members

Self assessment questions

1. Have you dealt with or performed Quality Risk Management in your establishment?
2. Is Quality Risk Management mandatory for an establishment required to comply with GMP guidelines?
3. Does the Risk Assessment need to be performed by a QRM expert?

Learning objectives

- Describe the GMP-requirements on risk analysis
- Outline challenges and limit risks as related to corrective and preventive actions (CAPA)
- Relate the number of patient cases with the importance of the risk
- Implement a suitable risk prevention activity in a hospital
- Perform an FMEA for the assortment issued from own production

Why QRM?

- Systematically prevent or reduce risks to product quality
- Reduce likelihood of harm to patients
- Legal requirements and state of the art production

GMP / legal requirements

- Recent changes in relevant chapters of EU GMP Guidelines (chapter 3 “Premises and Equipment”, chapter 5 “Production”, Annex 2 “...biological active substances...”,)
- ICH Q9 as part of the EU GMP Guidelines (Part III)
- Principles expressly stated (eg A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured.)

Biological Active Substances

- EC / PICS GMP Guidelines for biological active substances (Annex 2) “...quality risk management (**QRM**) principles are **particularly important** for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.

GMP / legal requirements

- EC Guidelines for ATMPs (May 2018)

“The level of effort and documentation should be commensurate with the level of risk. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.”

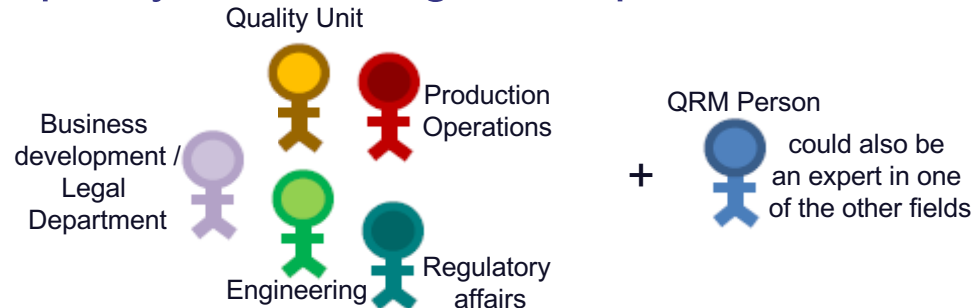


Definition of Risk/Challenges

- Risk is generally defined as the the combination of the probability of occurrence of *harm* and the *severity* of that harm
- $R = P \times S$
- In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.
- $R = P \times S \times D$
- Problem of subjectivity – how are the numbers determined?

Principles

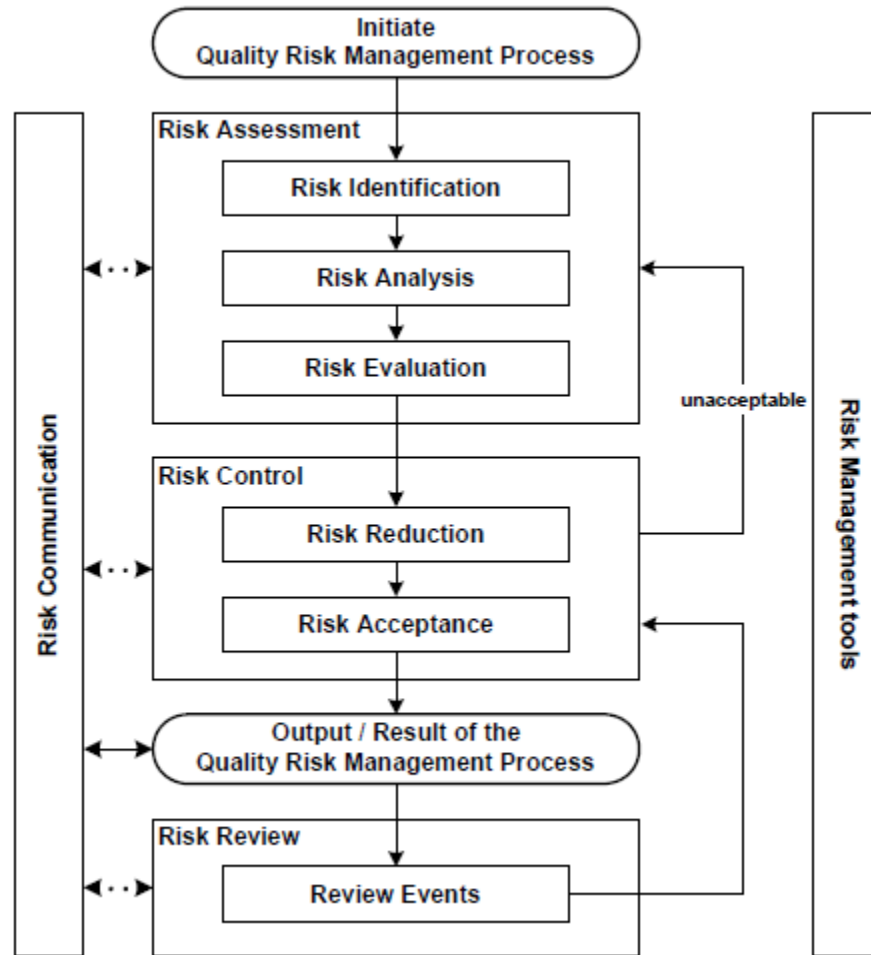
- Quality risk management activities are usually, but not always, undertaken by **interdisciplinary teams**. When teams are formed, they should include **experts from the appropriate areas** [...] in addition to individuals who are knowledgeable about the quality risk management process.



Principles

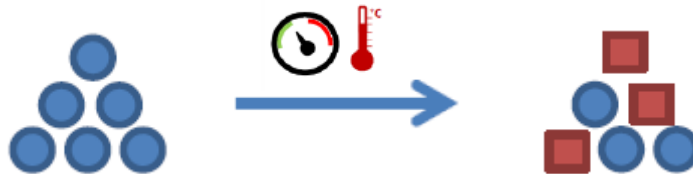
Decision makers should

- take responsibility for coordinating quality risk management across various functions and departments of their organization; and
- assure that a quality risk management process is defined, deployed and reviewed and that adequate resources are available.



Risk Identification

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences.



Risk Analysis

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.



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Risk Evaluation

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

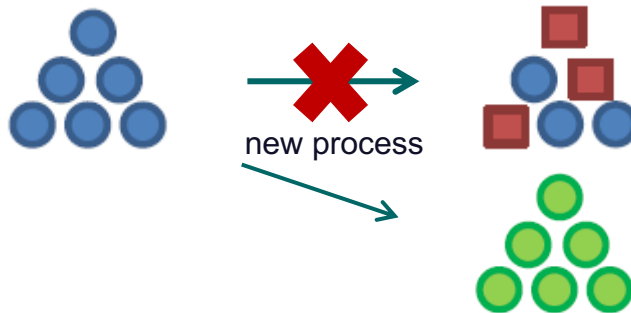
1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The **amount of effort** used for risk control should be proportional to the significance of the risk...

Risk Control / Questions

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

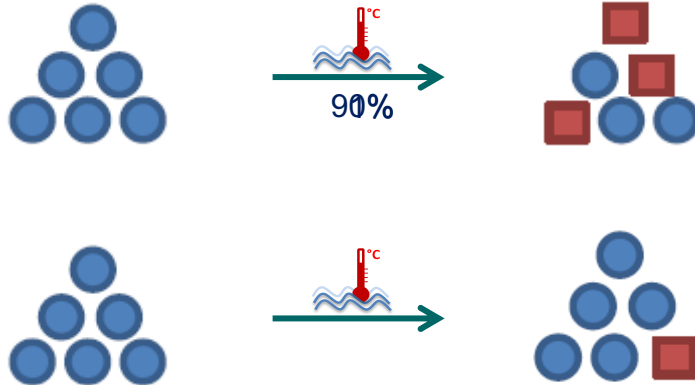


Risk Reduction

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include **actions taken to mitigate** the **severity and probability** of harm. Processes that **improve** the **detectability** of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks.

Risk Reduction

Corrective and Preventive Actions to decrease probability of occurrence or severity



Risk Acceptance

Risk acceptance is a decision to accept risk. Risk acceptance can be a **formal decision** to accept the residual risk or it can be a **passive decision** in which residual risks are not specified. For some types of harms, even the best quality risk management practices **might not entirely eliminate risk**. In these circumstances, it might be agreed that an appropriate quality risk management strategy applied and that quality risk is reduced to a specified (acceptable) level.

FMEA

- One of multiple systems of QRM described in ICH Q9
- Most popular and common in pharmaceutical environment

Example of an FMEA

- Manufacture of a sterile product. Process from washing to sterilization and filling.
- RPNs have been calculated for each step in the process and for critical areas.
- CAPAs have been developed and initiated for risks that were deemed unacceptable (RPNs too high)

Example of an FMEA

Definition and Determination of Numbers and Figures

Severity	
1	No impact on patient health
2	Low impact on patient health
3	Moderate impact on patient health
4	Serious impact on patient health
5	Very serious impact on patient health

Example of an FMEA

Definition and Determination of Numbers and Figures

Probability	
1	Very unlikely to occur
2	Unlikely to occur
3	Possible occurrence
4	Likely to occur
5	Very probable occurrence

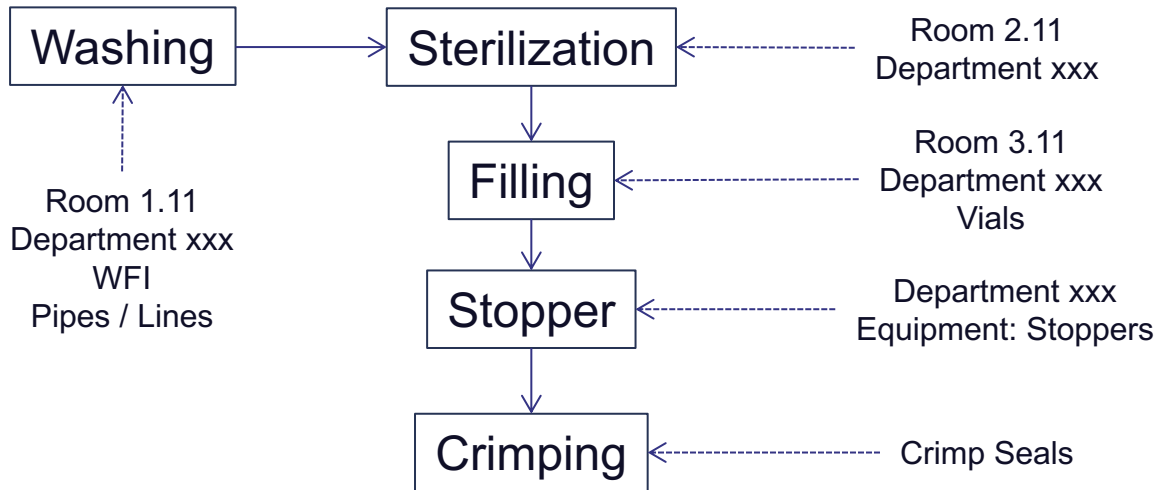
Example of an FMEA

Definition and Determination of Numbers and Figures

Detectability	
1	Easy detection
2	Very likely to detect
3	Likely to detect
4	Unlikely to detect
5	Very likely to detect

Example of an FMEA

Process of a sterile filling line



Example of an FMEA

Calculation of Risk Prioritization Number (RPN)

$RPN = \text{Severity (S)} \times \text{Probability (P)} \times \text{Detectability (D)}$

Cutoff needs to be defined between acceptable / unacceptable

RPN this case: **high**: ≥ 15 , **medium** ≥ 10 , **low** $< 10\#$

- RPN reasonable?

Sterilization								after CAPA			
Function	Subfunction	Risks	P	S	D	RPN	CAPA	P	S	D	RPN
Laminar Flow Unit	Heating / Cooling	- no filter integrity - partial pressure before / after filter too high	3	4	3	36	1. Regular filter integrity test 2. Alarm set for partial pressure display 3. Alarm set for flow controller	1	4	1	4
Temperature control	Radiant heater	decreased heating performance	2	2	3	12	1. Qualification of sterilization tunnel 2. Temperature monitoring 3. Automated stop when temperature falls below threshold	1	2	1	2
Depyrogenation process	Sterilization	Microbial contamination of product	3	4	2	24	1. High process temperatures and testing of endotoxin reduction during PQ	1	4	2	8
Premises	transition of vials from clean room D to clean room A	Microbial contamination	3	4	2	24	1. Installation of sterilization tunnel. Changed process as to keep vials in clean room A until crimping	1	4	2	8

Premises								after CAPA			
Function	Subfunction	Risk	P	S	D	RPN	CAPA	P	S	D	RPN
Clean Room D	Air handling	Breakdown	2	2	3	12	1. Control of air handling system linked to alarm 2. Permanent air pressure monitoring	1	2	1	2
Clean Room A/B	Grade A/B	Breakdown Laminar Air Flow Unit	2	5	3	30	1. Installation of separate motors, display of functionality 2. Manual checks of air flow	1	5	1	5
		Out of range humidity	2	3	1	6		n/a	n/a	n/a	n/a
		Exceeding particle count	2	5	4	40	1. Installed exhaust near floor 2. High air exchange rate 3. Constant monitoring of particles	1	5	1	5

Take home messages

- A Quality Risk Management system is mandatory for sites that have to comply with GMP
- FMEA is an easy to use tool to manage risks for a wide scope of products / processes
- Process knowledge is key to address risks appropriately
- Scientific knowledge and experience with the processes is important to rank risks accordingly

Self Assessment Q&A

1. Have you dealt with or performed Quality Risk Management in your establishment? – No wrong answer.
2. Is Quality Risk Management mandatory for an establishment required to comply with GMP guidelines? – Yes, regardless of type of product.
3. Does the Risk Assessment need to be performed by a QRM expert? – No, not necessarily, preferably an interdisciplinary team works on all stages of QRM together with a person knowledgeable in QRM

Questions

